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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,901	06/04/2001	Habib Zaghouani	8114-006-US	5455

32301 7590 01/10/2006

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,901	ZAGHOUANI, HABIB	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-22,26-59 and 62-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-22, 26-59, and 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 18, 2005 has been entered.

Claims 1-18, 23-25, 60, 61, and 66-68 are canceled.

Claims 19, 34, 40, 49, 55, 64, and 65 have been amended.

Claims 19-22 and 26-65 are pending and under examination in this office action.

It is noted that the claim set submitted October 18,2005, does not indicate that claims 60 and 61 have been canceled. In fact, claims 60 and 61 are not recited in any form. As such, claims 60 and 61 have been interpreted as being canceled since they are not present in the most recent claim set nor have they been present in the preceding claim sets examined as part of the office actions mailed July 23, 2004 and June 16, 2005. As such, any claim set submitted in reply to this office action should indicate that claims 60 and 61 are canceled. If applicant wishes to reintroduce the limitations found in these claims, they should be submitted as new claims starting with claim number 69.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 19-22, 26-59, and 62-68 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 10/277,264 for the reasons of record set forth in the office actions mailed July 23, 2004 and June 16, 2005.

Applicant's arguments filed October 18, 2005 have been fully considered but they are not persuasive. Applicant argues that the rejection is improper on two grounds. First, that the instant methods and copending methods administer different agents and second, that said agents work via different mechanistic pathways. The examiner is puzzled by applicant's argument that the administered agent is different, since

Examples I-XXIV are the same between the two applications and these examples make use of the agents Ig-PLP1 and IgPLP-LR. It is also noted that the additional experiments disclosed in the instant application continue to utilize Ig-PLP1. Since Ig-PLP1 is the same in both applications, how can it be that the administered agents are different? Further, the structure of an agent or composition is what is responsible for the therapeutic or mechanistic effects that occur upon administration to a patient. Since the structure is the same, any mechanism of action must be the same. Further, knowledge of how or why a therapeutic agent works is not required to demonstrate that said therapeutic agent is indeed effective in treating a disease or condition, and as already discussed, the mechanism by which an agent works is inherent in the structure of the agent itself.

The rejection or record is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 34-39, 41-54, 56-59, and 62-65 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons of record set forth in the office actions mailed July 23, 2004 and June 16, 2005.

Applicant's arguments filed October 18, 2005 have been fully considered but they are not persuasive. Applicant argues that the rejection should be withdrawn since the claims have been narrowed in scope to methods of alleviating symptoms associated with an autoimmune disease wherein the autoimmune disease is multiple sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis. Examination of the claims indicated that while the indicated diseases are a limitation of claims 19-22, 26-33, 40, and 55, they are not a limitation found in claims 34-39, 41-54, 56-59, and 62-65, and as such claims 34-39, 41-54, 56-59, and 62-65 still read on any and all autoimmune diseases. Applicant also argues that the recitation that the antigen is specific for autoreactive T cells associated with an autoimmune disease that has been introduced into independent claims 19, 34, 49, 64, and 65 is another reason to withdraw the rejection of record. The recitation that the antigen is specifically recognized by autoreactive T cells removes some issues, but problems remain. Specifically, autoimmune diseases are characterized by a phenomenon known as epitope spreading, wherein the number and identity of the antigenic epitopes recognized by autoreactive T changes and is enlarged as the disease progresses (Mamula, MJ, Immunological Reviews, 1998, 164:231-239, see entire document). Due to epitope spreading and the fact that the claims read on any autoimmune disease, the genus of antigens to be used in applicant's method is quite large and potentially unknowable since the claims encompass any newly identified

autoimmune disease in addition to well known diseases such as multiple sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis. Applicant has argued that since the structure of antibodies is well known and since some autoantigens in some autoimmune diseases have been well characterized, these limited examples convey to fusion proteins comprising antibodies and all antigens recognized by autoreactive T cells in all autoimmune diseases. Applicant is not in possession of the full scope of fusion proteins comprising all antigens recognized by autoreactive T cells in all autoimmune diseases because all such antigens are not known, and the identity of these unknown antigens cannot currently be predicted. As such, the rejection is maintained.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 34-37, 43-52, 58, 59, and 62-68 stand rejected under 35 U.S.C. 102(b) as being anticipated by Zanetti et al. (WO 90/09804A1, of record, see entire document), for the reasons of record set forth in the office actions mailed July 23,2004 and June 16, 2005.

Applicant's arguments filed October 18, 2005 have been fully considered but they are not persuasive. Applicant argues that the mechanism by which the engineered

immunoglobulins disclosed by Zanetti et al. function is different from the way in which the engineered immunoglobulins of the instant invention work in the recited methods, and that "Zanetti et al. does not, in fact, disclose a construct in which an immunoglobulin is linked to an antigen." Applicant's second argument will be addressed first since it will clarify the issues surrounding applicant's first argument.

Applicant has argued that applicant's invention "consists of having an immunoglobulin or a portion thereof linked to an antigen" and that Zanetti et al. do not teach such a construct. The examiner is puzzled by this argument, since applicant states on the record that Zanetti et al. teach a construct wherein a foreign epitope is introduced into the CDR3 of an antibody. The working examples disclosed by the instant specification all appear to utilize the Ig-PLP1 and Ig-PLP-LR constructs, which are antibodies that have a foreign peptide epitope inserted into CDR3. Is applicant arguing that the instant specification contains no working examples of the instant claimed invention? Applicant additionally indicates that the invention of Zanetti et al. is different from the instant invention in that Zanetti et al. introduces a foreign epitope *into* the CDR3 loop while the instant invention *deletes* the CDR3 loop and replaces it with a foreign peptide epitope. This is a mischaracterization of the teachings of Zanetti et al., which clearly indicate on line 24 of page 22 that the peptide epitope can be inserted or *substituted* for a CDR loop sequence. Thus, Zanetti et al. do teach the replacement of CDR3 loop sequences with foreign peptide epitopes. As such, it appears that the structure of the constructs taught by Zanetti et al. and the structure of the constructs taught by the instant specification are the same. Since the structure of these constructs

is the same, the mechanism of action will inherently be the same since function is dependent upon structure.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Further, in In re Crish, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." See also MPEP 2112.

It does not matter that Zanetti et al. teach that their constructs work differently from the instant invention, since the mechanism by which the constructs achieve the goal of treating autoimmune diseases is a characterization of the prior art construct and a scientific explanation for its function. Even if the mechanism disclosed by Zanetti et al. is not the most important pathway by which these constructs exert their therapeutic properties, or even if their explanation is assumed to be completely wrong, it would not alter the fact that the constructs of Zanetti et al. appear to be structurally identical to the Ig-PLP1 and Ig-PLP-LR constructs of the instant invention. The same structure must give rise to the same function and mechanism of action, even if it is not disclosed, and as such the rejection is maintained.

The following are new grounds of rejection

Claim Rejections - 35 USC § 102

8. Claims 19-22, 28, 29, 32-40, 43, 44, 47-55, 58, 59, and 62-65 are rejected under 35 U.S.C. 102(b) as being anticipated by De Boer et al. (WO 95/32734A1, see entire document).

De Boer et al. teach compositions and methods for treating autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and type I diabetes mellitus (see entire document, particularly the abstract and lines 14-18 of page 22). The compositions used in these methods of treatment consist of an antigen combined with an agent capable of crosslinking Fc_γ receptor molecules (see particularly lines 6-25 of page 14). Antigens disclosed for use include disease autoantigens (see particularly lines 3-5 of page 15), and the Fc receptor crosslinking agent can be aggregated human IgG, Fc domains of human IgG, bi- or multivalent anti-Fc_γ receptor monoclonal antibodies or active fragments thereof, and recombinant fusion proteins (see particularly the abstract, the paragraph that spans pages 11 and 12, and claims 1-35). The antigen and Fc receptor crosslinker are disclosed as being attached or aggregated by any technique known in the art, such as covalent chemical crosslinking and the generation of recombinant fusion proteins (see particularly lines 10-15 of page 14 and lines 14-16 of page 15). These reagents are also disclosed as being immobilized in a lipid matrix (see particularly lines 23-31 of page 13).

Note that the instant application defines chimeric more broadly than what is customary in the art, such that any fusion protein comprising an Fc domain and a heterologous sequence, such as an antigen, is considered by applicant to be a "chimeric antibody" (see particularly the paragraph that spans pages 38 and 39 of the instant specification). As such, the fusion polypeptides disclosed by De Boer are "chimeric antibodies." It is also noted that some of the instant claims indicate a need to identify individuals in need of increased levels of IL-10 or in need of reduced IFNγ, and that the art of De Boer does not appear to discuss these cytokines. However, the instant specification discloses that IL-10 inhibits the activity of T cells specific for multiple epitopes involved in autoimmune diseases, and as such any person suffering from an autoimmune disease is in need of increased IL-10 (see particularly the paragraph that spans pages 44 and 45). Further, it is well known in the art that IL-10 is an inhibitor of Th1 cytokines, that IFNγ is a Th1 cytokine, that Th1 cytokines are involved in inflammatory immune responses, and that the destruction of myelin sheaths in MS, synovium erosion in rheumatoid arthritis, and islet cell destruction in type I diabetes mellitus are all inflammatory reactions. As such, a medical diagnosis that a patient has multiple sclerosis, rheumatoid arthritis, or type I diabetes mellitus inherently identifies individuals that need increased IL-10 and decreased IFNγ.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 19, 30, 31, 34, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Boer et al. (WO 95/32734A1, see entire document) in view of Zanetti et al. (WO 90/09804A1, of record, see entire document).

The teachings of De Boer et al. have been discussed above. These teachings differ from the instant claimed invention in that while De Boer et al. teach methods of treating autoimmune diseases using conjugates comprising an Fc receptor crosslinker and an autoantigen, they do not indicate that the autoantigen is to be located in the CDR3 loop of an antibody.

Zanetti et al. teach that the introduction of an antigen into the CDR3 loop of an antibody offers the advantage of a construct that maintains immunoglobulin constant domain functionality yet contains novel epitope reactivity with the CDR3 loop being preferred because it is surface exposed and is structurally plastic since it is known to naturally contain sequences of diverse length and amino acid composition (see entire document, particularly the abstract, lines 7-25 of page 5, and the paragraph that spans pages 10 and 11).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to insert autoantigens into the CDR3 lops of the constructs disclosed by De Boer et al. in order to gain the advantages of maintained constant domain effector function, epitope reactivity, structural plasticity and surface exposure of the autoantigen epitope as taught by Zanetti et al.

11. Claims 19, 26, 27, 34, 41, 42, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Boer et al. (WO 95/32734A1, see entire document) in view of Legge et al. (J. Exp. Med. 1997, 185:1043-1053, see entire document).

The teachings of De Boer et al. have been discussed above. These teachings differ from the instant claimed invention in that while De Boer et al. teach methods of treating the disease multiple sclerosis with compositions comprising autoantigens, they do not teach the specific multiple sclerosis autoantigens proteolipid protein (PLP) or myelin basic protein (MBP).

Legge et al. teach that PLP and MBP are major autoantigens recognized by autoreactive T cells from patients suffering from multiple sclerosis (see entire document, particularly the introduction). They also teach the use of these autoantigens in antibody fusion constructs offer the advantage that these autoantigens are presented to the immune system in a manner that is capable of eliciting an immune response to a self antigen (see particularly the discussion and Figures 1-9).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to use the specific multiple sclerosis autoantigens PLP and

MBP as taught by Legge et al. in the therapeutic constructs taught by De Boer et al. to gain the advantage of using major autoantigens that are known to be recognized by the immune system when presented in a fusion construct comprising an antibody and said autoantigens.

Double Patenting

12. Claims 19-22, 26-59, and 62-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 10/847,139. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application are narrower in scope and thus anticipate the instant invention. This is because the copending claims specify that an antigenic peptide is a T cell agonist or antagonist that must be located within complementarity determining region of an antibody and thus they are narrower than the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 19-22, 26-59, and 62-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 10/681,788. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application are narrower in scope and thus anticipate the instant invention.

This is because the copending claims specify that the administered composition is to be used in treating type I diabetes mellitus, and thus they anticipate the broad genus of autoimmune diseases recited in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 19-22, 26-59, and 62-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/290,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application are narrower in scope and thus anticipate the instant invention. This is because the copending claims specify that the administered composition is to be used in treating type I diabetes mellitus, and thus they anticipate the broad genus of autoimmune diseases recited in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/7/06